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(54) **METHOD FOR OBTAINING SOLID MICRO -OR NANOPARTICLES**

(57) The invention provides a novel method for obtaining solid micro -or nanoparticles with a homogenous structure. A method is provided for obtaining solid micro -or nanoparticles with a homogenous structure having a particle size of less than 10 μm where the processed solid compound has the natural, crystalline, amorphous, polymorphic and other features associated with the starting compound. In accordance with the invention a method which also makes it possible to obtain solid micro -or nanoparticles with a substantially spheroidal morphology is provided.

EP 2 383 034 A1

Description

FIELD OF THE INVENTION

[0001] This invention provides a process to obtain solid micro- or nanoparticles with a homogenous structure from a microemulsion.

[0002] According to the invention, it provides a process which allows to obtain solid micro- or nanoparticles of a homogenous structure, with a size of a particles of less than 10 μm in which the solid processed compound reveals the nature, e.g., crystalline, amorphous, polymorphic, etc..., typical of the original compound. According to the invention process, sizes as small as 500 nm can be obtained. Advantageously, the invention provides a process to obtain for obtaining solid micro- or nanoparticles with an aspect ratio close to the unity (1), i.e., with a substantially spheroidal morphology.

BACKGROUND OF THE INVENTION

[0003] There are in the state of the art different processes that refer to obtaining particles finely divided as a strategy to increase their water solubility and, therefore, the bioavailability of active molecules in physiological conditions. Some of these processes have used as a model molecule, ibuprofen to show their effectiveness in this way. Below, are some details of the work based on experiments with ibuprofen.

[0004] The article by N. Rasenack, B. W. Müller, Pharmaceutical Research, 2002, 19, 1894-1900, proposes the use of a technique called in-situ Micronization as an alternative to the conventional techniques of micronization by grinding to obtain micro- and nanoparticles of solids slightly insoluble in water such as ibuprofen. To form the particulate solid an aqueous solution is poured in a stabilizing agent over a solution of ibuprofen in an organic solvent miscible in water. In this process water acts as a non-solvent of the product causing its precipitation and producing a suspension of it. This precipitation is followed by a process of "spray drying" to eliminate the liquid from said suspension and isolating the particulate solid. This solid consists of microparticles of the active principle coated with the stabilizing agent.

[0005] In the article by M. Charoenchaitrakool, F. Deghani, N. R. Foster, Ind. Eng. Chem. Res. 2000, 39, 4794-4802 racemic ibuprofen and S-ibuprofen have been micronized by the RESS process described in patent US 4582731. This process consists in the depressurization of a solution of a product (ibuprofen) in a supercritical fluid (CO_2) through a nozzle, causing its precipitation. Microparticles of the product (1-15 μm) are obtained with an irregular geometry and with a considerable loss in crystallinity.

[0006] In the article by D. Hermsdorf, Stephan Jauer, R. Signorell, Molecular Physics, 2007, 105, 8, 951-959, racemic ibuprofen and S-ibuprofen have also been micronized using the process RESS. Particles of pure ibuprofen strongly agglomerated and coagulated which consist of primary particles of 100-500 nm with irregular shapes.

[0007] The article by P. Pathak, M.J. Meziani, T. Desai, Y.-p. Sun, J. Supercrit. Fluids, 2006, 37, 279-286 describes how to obtain suspensions in water of not-agglomerated ibuprofen particles at a nanometric scale by using the RESOLV process. This process consists in depressurizing the RESS method over an aqueous solution obtaining the stabilization of particles in the aqueous medium which can contain a surfactant. This process is described in patent applications W09965469 and W09714407.

[0008] However, it is often desirable to obtain solid particles finely divided with a greater control of the particle size.

[0009] Mainly, three methodologies have been developed to prepare finely divided solid particles based on the use of emulsions and CO_2.

[0010] In the first methodology, the synthesis of the particles is done by an anti-solvent effect of the CO_2 ("anti-solvent gas", GAS) over an emulsion of the solute to be precipitated. This methodology has been developed by Zhang et al., and comprises two stages: In the first stage, an emulsion of water in a non-polar solvent (usually isooctane) is prepared which contains the solute to be precipitated and a surfactant, both dissolved. The second stage consists in the precipitation of the particles when the emulsion comes into contact with the CO_2. This methodology is described, e.g., J. Zhang, B. Han, X. Zhang, J. He, Z. Liu, T. Jiang, G. Yang, Chem Eur. J. 2002, 8, 17, 3879.

[0011] The second methodology, called "supercritical fluid extraction emulsion" (SFEE), is based in the precipitation of particles from the extraction by CO_2 of the non-polar solvent which is a part of the emulsion. This methodology has been developed by "*Ferro Corporation*" (US2004071781). In this process, the synthesis of the particles also comprises two stages. In the first one, called preparation of the emulsion, the solute to be precipitated is dissolved in a non-polar saturated solvent with water. On the other hand, the surfactant is dissolved in saturated water with the same non-polar solvent. Next, both solutions are mixed to form an emulsion. Finally, the resulting emulsion is homogenized in a homogenizer. In the second stage, the precipitation of the particles takes place. The emulsion is pulverized through a nozzle in an extraction column through which CO_2 circulates in a counter-current flow. The emulsion droplets come into contact with the CO_2, and it extracts the non-polar solvent from the emulsion. The particles will precipitate into fine particles suspended in the aqueous phase. Therefore, through this technology the precipitation of the particles takes place by

the extracting effect of the non-polar solvent which causes the precipitation. Within this methodology, based on the extracting role of CO_2, *Inserm Inst Nat Sante & Rech Medicale* (WO2007072106) a new process has been developed to prepare the particles. This process is based in the extraction of the organic solvent of the emulsion by the CO_2, upon changing it from critical conditions to a liquid state. The particles' synthesis comprises the preparation of an emulsion, and the solidification of the discontinuous phase to form the particles. The emulsion will be made up by a compressed fluid (continuous phase), and a solvent which will contain the solute to be precipitated dissolved (discontinuous phase). The compressed fluid will extract the solvent from the discontinuous phase, upon changing from critical conditions to liquid state, therefore precipitating the particles.

[0012] The third particle precipitation methodology is based on the use of emulsions made up of water as a discontinuous medium and CO_2 as the continuous medium ("water-in-CO_2 emulsions"). In this methodology there can be two types of different precipitations. In the first place, there is the one developed by "Ferro Corporation" (W02004110603) which is based in the pulverization of an emulsion made up of water and CO_2 within a reactor, and a later elimination of the solvents so as to finally obtain the particles. The synthesis comprises three stages. In the first one, an emulsion is prepared. The continuous phase will be made up by compressed fluid or supercritical (CO_2), and the discontinuous phase by a solution (preferably aqueous) of the solute to be precipitated and/or reacted. In a second stage, the emulsion is pulverized through a nozzle forming small droplets of emulsion. In a third stage, the compressed fluid and the organic solvent from the droplets is eliminated which leads to the precipitation of the particles. In second place is the use of emulsions made up of water as a discontinuous medium and CO_2 as the continuous medium. In this case, the method of precipitation is based in the precipitation of the particles from a mixture of two emulsions water/CO_2. The synthesis of the particles comprises two stages: In a first stage two emulsions are prepared. The continuous phase is made up of compressed fluid or supercritical (CO_2), and the discontinuous phase by the solution (preferable aqueous) of the solute to be precipitated and/or reacted. In a second stage, the two emulsions are mixed and their components react precipitating the particles. The article by C.A. Fernandez, C.M. Wai, Small 2006, 2, 11, 1266, describes how to obtain the silver nanoparticles through this methodology.

[0013] However, in many occasions it is desirable to obtain solid micro- or nanoparticles with a high homogeneity in the size of the particle and with a greater control of it. Besides, in most existing techniques to date the nature of the initial product does not manifest in the same way in the final processed product, loosing or reducing, e.g., their crystalline nature in the final product.

[0014] Therefore, there isn't yet a technology which allows to reduce the size of the particle which allows a greater control and homogeneity of it and which at the same time allows the very own properties, e.g., crystalline, of the nature of the initial product to manifest in the solid micro- or nanoparticles obtained after processing.

Summarized Description of the invention

[0015] To said purpose, this invention provides a process to obtain solid micro- or nanoparticles from a microemulsion. The microemulsions are **characterized in that** they are thermodynamically stable; they form spontaneously with the average diameter of the nanometric droplets and by being transparent or bluish translucent.

[0016] The process to obtain the solid micro- or nanoparticles is based on providing a microemulsion which includes water (H_2O), an organic solvent or a mixture of organic solvents, a solid compound C and a fluid compound B, where said micro- or nanoparticles obtained posses a homogenous structure with a particle size that can reach values as low as 500 nm. According to the invention, the precipitation of the solid micro- or nanoparticles is done by the anti-solvent effect of water without requiring a highly effective agitation system. The process of the invention allows to directly obtain micro- or nanoparticles of a homogenous structure, which manifest the very own properties of the nature of the initial product, e.g., crystallinity, amorphousness, polymorphism, etc..., in the processed product and optionally have an aspect ratio close to the unity (1), i.e., have a substantially spheroidal morphology, and size of particle comprised between 10 μm and 500 nm.

[0017] A first aspect of this invention is to provide a new process to obtain solid micro- or nanoparticles of a homogenous structure. Said process comprises preparing a mixture which includes an organic solvent or a mixture of organic solvents, a solid compound C and water (H_2O), and obtain a microemulsion by adding a fluid B, and increasing the pressure until reaching a first pressure (P_1) where the predetermined supersaturation value (β) of the solid compound C is lower or equal to 1. Next, a variation of said first pressure (P_1) to a second pressure (P_2) allows to modify the solvent effect of water (H_2O) in said first pressure (P_1) to an anti-solvent in said second pressure (P_2) which causes the precipitation of solid micro- or nanoparticles of a homogenous structure; Next, they can be isolated and collected at said second pressure (P_2) said solid micro- or nanoparticles using conventional methods.

[0018] Advantageously, with the process according to the first aspect of the invention micro- or nanoparticles with an improved stability are provided, i.e., with a lower risk of degradation or structural change during their storage, less reactivity and greater stability to mechanical or thermal stress, besides a lower sensibility to humidity.

[0019] A second aspect of this invention is the use of said improved micro- or nanoparticles in a composition which

also comprises other acceptable pharmaceutical excipients. Advantageously, according to the process other the invention solid micro- or nanoparticles of a homogenous structure, crystalline and with an aspect ratio close to the unity can be obtained, i.e., of a spheroidal morphology, which makes them useful to applications where the structure and morphology of the particles has a decisive influence for their administration.

[0020] A third aspect of this invention is the use of said micro- or nanoparticles of homogenous structure and with an aspect ratio close to the unity for the preparation of aerosols based on active principles of use via inhalation or for preparing suspensions of a therapeutically active principles which have low hydrosolubility and bioavailability.

Definitions

[0021] In this invention, **"fluid B"** refers to a fluid which at atmospheric pressure and room temperature is a gas and which at a first pressure (P_1), greater than atmospheric pressure, is miscible with the organic solvent, and immiscible or partially miscible with water. Preferably, said fluid B is selected from CO_2 and Freon. Besides, according to the pressure and temperature conditions according to the process of the invention said fluid B does not act as a supercritical fluid in any of the stages defined in the attached claims.

[0022] In this invention "**organic solvent**" refers to any polar or apolar organic solvent or mixture of both that is miscible with CO_2 at a first pressure (P_1), higher than the atmospheric pressure, and miscible with water at atmospheric pressure.

[0023] Preferably, said organic solvent can be selected from the group comprised by: monohydric alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 1-hexanol, 1-octanol and trifluoroethanol, polyhydric alcohols such as propylene glycol, PEG 400, and 1,3-propanediol; ethers such as tetrahydrofuran (THF), and diethyl ether, alkanes such as decalin, isooctane, and mineral oil; aromatics such as benzene, toluene, chlorobenzene, and pyridine, amides such as n-methyl pyrrolidone (NMP), and N,N-dimethylformamide (DMF); esters such as ethyl acetate, propyl acetate, and methyl acetate, 1,2-dichloroethane, and 1,1,1-trichloroethane, ketones such as acetone, methyl ethyl ketone, and Methyl isobutyl ketone; other solvents such as ethylenediamine, acetonitrile, and trimethyl phosphate. Solvents with low volatility such as dimethylacetamide or dimethyl sulfoxide or an ionic liquid can also be used. In an embodiment of the present invention, the preferred organic solvent is acetone.

[0024] In this invention **"surface active agents"** or "surfactant" refers to an anionic, cationic or neutral agents which can be selected among an emulsifying agent, surface agent, stabilizing, protective colloid and, more preferably, from among, the polyethylene glycols (PEGs), the polysorbates, poloxamer, ascorbyl palmitate, lecithin, hexadecyltrimethylammonium bromide (CTAB), sulphates, sulfonates, phosphates, carboxylates, and sulfosuccinates. Yet more preferably, selected from among polyethylene glycols 6000 (PEG6000), bis (2-ethylhexyl) sodium sulfosuccinates (AOT), sodium dodecyl sulphate (SDS), Sodium octyl sulphate, sodium tetradecyl sulphate, octadecyl sodium sulphate, sodium laurate, cholesterol sulfate sodium salt, sodium dodecyl sulfonate, sodium decyl sulfonate, sodium octyl sulfonate, sodium oleate, as well as among others, or a mixture of thereof.

[0025] In this invention "**aspect ratio**" (RA) refers to a value close to 1, where said value has the sole purpose of defining a particle commonly called of a spheroidal morphology. The aspect ratio can be commonly defined as the relationship between the length and height of the particle, where the length is the greatest distance when measured between two points of the perimeter of the projection of the particle independent of its orientation and width is the greatest distance between two points contained in the intersection of one of the perpendicular axis to the length and perimeter according with the process defined in S.Almeida-Prieto, J. Blanco-Mendez, F.J. Otero-Espinar, European journal of Pharmaceutics and Biopharmaceutics 67 (2007) 766-776, particularly, page 772, Figure 5, process (a), of Research paper *"Microscopic image analysis techniques for the morphological characterization of pharmaceutical particles: influence of the software, and the factor algorithms used in the shape factor estimation"* based on the determination of which the value of the aspect ration is indicated in this invention, without this meaning that other methods can not be used to define a particle with a spheroidal morphology.

[0026] In this invention "**solid compound C**" refers to a substance or mixture of solid substances, selected from a drug, explosive, colorant, pigment, cosmetic, polymer, catalyst, chemical product for the agriculture or other particle or substance completely insoluble in water, and susceptible to being dissolved at the pressure at which the value of supersaturation (β) is less than or equal to 1, where the temperature is within the margins described later according to the invention.

[0027] The formation of micro- or nanoparticles can be monitored and controlled by analysing the turbidity of the system, in turn induced by successive pressure changes and mole fraction of CO_2 (X_{CO2}) in the system. The turbidity of the system can be measured by optic density. The optic density (OD) is defined as the absorbance of an optic element at a determined wavelength in which the system does not absorb, and by unit of optical path or distance. The optical density is a property used in the invention to detect variations of the supersaturation value (β) in the system when $\beta \geq 1$, and of the supramolecular organization of its components. The "on-line" monitoring of the system is done by means of a UV visible Spectrophotometer.

Detailed Description of the Invention

[0028] According to the first aspect of this invention, a process is provided to obtain micro- or nanoparticles with a homogenous structure.

[0029] The process according to the first aspect of the invention comprises:

a) preparing in a closed container a mixture that includes an organic solvent or a mixture of organic solvents, a solid compound C and water

(H_2O),

where in said stage a) there are at least one liquid phase and one solid phase, **characterized in that** it also comprises:
b) adding a fluid B to said mixture prepared in stage a) so that the pressure of the container is increased until to reach to a first pressure (P_1), allowing said addition of fluid B at said first pressure (P_1) to prepare a microemulsion of an organic phase saturated with water,
where there is no solid phase in this stage and where at said first pressure (P1) the value of the predetermined supersaturation (β) of the solid compound C is lower to or equal to 1,
c) varying said first pressure (P_1) to a second pressure (P_2), where said variation in pressure is different from zero ($\Delta P \neq 0$), and where at said second pressure (P_2) said water (H_2O) has an anti-solvent effect which cause the precipitation of solid micro- or nanoparticles of compound C with homogenous structure;
where in said stage c) there are at least one liquid phase and one solid phase;
and, if desired;
d) collecting at said second pressure (P_2) said solid micro- or nanoparticles by conventional methods.

[0030] In said stages a), b) and c), the transition from one to another is determined by the phase changes observed through variations in the optic density.

[0031] Thus, en stages a) and c), the nature of the solvent will determine the existence of one or more liquid phases, depending on if it is a polar or non-polar organic solvent or mixtures of both or of more than one of them. In said stages a) and c) when a polar solvent is used there is a unique liquid phase. If a non-apolar solvent is used, there will be more than one liquid phases determined by optic density.

[0032] Advantageously, the mixture of stage a) is prepared at atmospheric pressure and room temperature. However, the temperature of the process, regardless of the stage, can be comprised between -50°C and 200°C, and yet more preferably between 20°C and 50°C.

[0033] Optionally, stages a) and b) can be carried out simultaneously. In this embodiment, where stages a) and b) are carried out simultaneously, the process continues to stage c). The increase in pressure of the container to the first pressure (P_1) in stage b) can be carried out whether by adding fluid B, the use of mechanical means such as, e.g., a piston inside the container, or by adding an inert gas, such as for example N_2. Also, the pressure variation in stage c) to a second pressure (P_2) can be done in the same way.

[0034] In yet another embodiment of this invention, in stage a) a surfactant can also be added. Advantageously, the presence of the surfactant in the microemulsion obtained in stage b) improves the stability of the final dispersion even more, which is capable of favouring the control of the nucleation processes and crystalline growth, thus, obtaining still smaller particle sizes and narrower size distributions.

[0035] It is worth pointing out that in stage b), when said first pressure (P_1) is reached, where the supersaturation value (β) the ratio between the concentration [C] of the solid compound C to the concentration of the supersaturation [C_s] of said solid compound C in the microemulsion:

$$\beta = [C]/[C_s] \quad \ldots 1$$

where said microemulsion is formed by said organic solvent or mixture of organic solvents, said water (H_2O) and said fluid B and, optionally, a surfactant.

[0036] The microemulsion formed in said stage b) comprises an organic phase saturated with water, where said organic phase is formed by said fluid B, said organic solvent or a mixture of organic solvents and said solid compound C and optionally, said surfactant.

[0037] The variation of the first pressure (P_1) to the second pressure (P_2), where said positive or negative pressure variation, i.e., increasing or decreasing the first pressure (P_1) to a second pressure (P_2), stimulates the precipitation of

the solid micro- or nanoparticles of homogenous structure due to the anti-solvent effect of the water (H_2O) at said second pressure (P_2), where the supersaturation value (β) is greater than 1.

[0038] Surprisingly, the authors of this invention have found that the final characteristics of the micro- or nanoparticles obtained do not depend in the effectiveness of agitation as is the case in the technologies described to date, but rather the degree of homogenous distribution of water in the microemulsion obtained which after a variation in the pressure (stage c)) causes the water to act as an anti-solvent and causes the precipitation of the solid micro- or nanoparticles. Therefore, the process of this invention represents a considerable change in the line followed up to now for obtaining finely divided particles based mostly in that a higher agitation or homogenization of the solution that contains the solid to be precipitated provides a smaller sized particle.

[0039] According to the present invention, the anti-solvent effect of water in determined pressure conditions and in an adequate medium, a microemulsion, allows to obtain solid micro- or nanoparticles of a homogenous structure whose micro- or nanoparticles also manifest the initial properties of the nature of the organic compound to be precipitated.

[0040] In an embodiment of the invention, when the pressure variation in stage c) is positive, i.e. $\Delta P>0$, the second pressure (P_2) is greater than the first pressure (P_1), and the precipitation is a reversible phenomenon.

[0041] In another embodiment of the invention, when the pressure variation in stage c) is negative, i.e. $\Delta P<0$, the second pressure (P_2) is lower than the first pressure (P_1) and the precipitation is an irreversible phenomenon.

[0042] According to the process of the invention, when $\Delta P>0$ the organic solvent can be selected from a polar or non-polar solvent and when $\Delta P<0$ the organic solvent is a polar solvent.

[0043] Next, the micro- or nanoparticles are collected at said second pressure (P_2) by conventional means. Optionally, said particles can be isolated and collected, e.g., by filtration and also when $\Delta P<0$ they can be collected over a water current so that a suspension of said particles is obtained. Said suspension has application in the preparation of a medicine preferably by oral, intravenous or mucosal administration.

[0044] With the pressure variation (stage c) of the microemulsion the behaviour of the water is modified, which goes from acting as a solvent at P_1 to acting as an anti-solvent at P_2 which causes the precipitation of the solid micro- or nanoparticles with a homogenous structure. In an embodiment of the invention, said solid micro- or nanoparticles are also crystalline. Also, in another embodiment of this invention said solid micro- or nanoparticles have an aspect ratio considerably equal to the unity (1).

[0045] Advantageously, with the process according to the first aspect of the invention micro- or nanoparticles are provided with an excellent aspect ratio-property. Thus, with the process of the invention micro- or nanoparticles with improved structural characteristics can be obtained such as, e.g., a greater crystallinity, which confers greater stability during storage, fluidity and less tendency to absorb humidity.

[0046] Furthermore, adding fluid B, for example CO_2 in the process of the invention and unlike those of the techniques described to date, does not cause the precipitation of the solid compound C in the form of finely divided particles.

[0047] With it, the process of the invention provides a new technology for obtaining solid micro- or nanoparticles where fluid B is not responsible for the precipitation, nor is it used in supercritical state in any stage of the process. It is believed that the anti-solvent effect of water at P_2 and the conditions in which the precipitation occurs favour a nucleation and growth of crystalline structure with a substantially spheroidal morphology. Thus, the new process provides unexpected properties to the micro- or nanoparticles obtained, properties not described in the state of the art at said micro- or nanoscale.

[0048] The crystallinity, and therefore, the absence of an amorphous solid in, e.g. a pharmaceutical product is of great importance because it is considered that formulas that contain amorphous forms are less stable than the crystalline solid and, therefore, carry a risk regarding its preservation of the properties of the material during storage. These partial or completely amorphous materials usually have greater reactivity and are unstable to mechanical and thermal stress and have a greater tendency to absorb water.

[0049] Furthermore, advantageously, according to the first aspect of this invention, a process for obtaining micro- or nanoparticles with a considerably spheroidal morphology, also called morphology with an aspect ratio close to 1, according to the method mentioned in the definitions section for aspect ratio.

[0050] Morphology is a highly determining property in the preparation and administration of, for example, a medicine which already has special effect in the properties of pharmaceutical formulation such as fluidity and compactness. Thus, the more regular and similar to the spherical form is the morphology of the particles the greater their fluidity in aerosol formulas, such as the ones used for oral administration.

[0051] The particles obtained have a narrow volumetric size distribution and an average associated sphere diameter of less than 10 μm, generally less than 1 μm. Advantageously, the size of the particle obtained with the process defined in the invention is comprised between 10 μm and 500 nm, preferably between 3 μm and 800 nm, more preferable between 1 μm and 700 nm.

[0052] Thus, according to the second aspect of the invention, the micro- or nanoparticles obtained according to the first aspect of the invention are of a great interest in the preparation of a composition which also comprises other acceptable pharmaceutical excipients where the structure and morphology of the micro- or nanoparticles is a determining

factor for their application.

[0053] Also, according to the third aspect of the invention said micro- or nanoparticles obtained are of special interest in the preparation of an aerosol for inhaled administration of medicines destined to the treatment of pulmonary diseases, or of other formulas where the purpose is to increase the bioavailability of active substances with low water solubility.

Description of the Drawings

[0054]

Figure 1 shows two curves of supersaturation with regards to time (t), curve A and curve B.
Said figure 1 has three different areas, area I where there is no crystal growth, area II where there is crystal growth but no nucleation and area III where there is nucleation. Curve A corresponds to a qualitative profile of supersaturation corresponding to a process of crystallization where the nucleation phenomenon is favoured above the crystal growth process. Curve B corresponds to a qualitative profile of supersaturation of a process where the crystal growth is favoured above the nucleation.
The process of the invention follows a supersaturation type A curve, which is **characterized in that** it takes place in area IIII in a brief period of time and, therefore, there is a high nucleation, with translates into a greater number of solid particles with a smaller size.

Figure 2 shows a facility to carry out the process of the invention. Said facility comprises a tank 1 which contains CO_2, said tank is connected to a pump 3 to supply said liquid CO_2 at high pressure. The adding of liquid CO_2 over the mixing reactor 7 where there is already a mixture of organic solvent (or a mixture of organic solvents), a solid compound C and water can be done through the uppermost part through valves 4 and 6, or through valves 4 and 5 through the lower part. Through valves 9 and 5, the addition to the mixing reactor 7 of an inert gas N_2, which is in tank 8, is controlled. This inert gas can be used to increase the pressure from P_1 to P_2 when $\Delta P_{(P2>P1)}>0$. Alternatively, a piston mechanically or pneumatically actuated (not shown) can be used to increase the pressure in mixing reactor 7. The microemulsion formed in reactor 7 at pressure P_2 passes to filter 11 through valve 10, where it undergoes the first filtration maintaining the pressure P_2. Upon exiting filter 11 and passing through valve 12, the microemulsion containing CO_2 is expanded and is rapidly depressurized to atmospheric pressure, with the consequent precipitation of the solid crystalline particles. During the filtration at atmospheric pressure in filter 13, the particles are retained in filter 13 and the mother liquor is collected in container 15 through valve 14.

Figure 3 shows the variation in optic density observed in a microemulsion formed according with the process of the invention, e.g., by the system "ibuprofen/acetone/water/PEG6000/CO_2" in function of the pressure at 35°C.
The optical density is defined as the absorbance of an optic element at a determined wavelength and by unit of optical path or distance. The turbidity of a system is defined in terms of optical density when the system does not absorb light at that wavelength.

Figure 4 represents a differential scanning calorimetry profile (DSC) of the solid compound C (ibuprofen) obtained according to the process of the invention, with or without a surfactant (PEG6000). From said figure it can be observed that the presence of the surfactant does not modify the crystalline structure of the solid micro- or nanoparticles nor does it affect it if $\Delta P_{(P2>P1)}<0$ or if $\Delta P_{(P2>P1)}>0$. Profile 1 corresponds to the ibuprofen compound obtained for $\Delta P_{(P2>P1)}>0$. in the presence of surfactant (PEG6000). Profiles **2** and **3** correspond to the ibuprofen compound obtained for $\Delta P_{(P2>P1)}<0$ with or without surfactant (PEG6000), respectively. Profile **4** corresponds to the original unprocessed ibuprofen. In Figure 4 symbols X and Y correspond to the fusion endothermic peaks of the surfactant (PEG6000) and compound C (ibuprofen), respectively.

Figure 5 represents a X-ray diffraction spectrum of solid compound C (ibuprofen) obtained using the process of the invention in presence or absence of surfactant (PEG6000). Particularly, in said figure it can be observed that with the process according to the invention, solid crystalline micro- or nanoparticles are obtained whether $\Delta P_{(P2>P1)}<0$ or $\Delta P_{(P2>P1)}>0$. The spectrums **(a)** and **(b)** correspond to the ibuprofen compound obtained for $\Delta P_{(P2>P1)}<0$ with or without surfactant (PEG6000), respectively. Spectrum **(c)** corresponds to the ibuprofen compound obtained for $\Delta P_{(P2>P1)}>0$ with surfactant (PEG6000). Spectrum **(d)** corresponds to the original unprocessed ibuprofen compound.

Figure 6A is an image of a scanning electron microscope (SEM) of the ibuprofen compound obtained without surfactant and $\Delta P<0$ (P2<P1).

- Ibuprofen/acetone/water/CO_2, without surfactant;

- Precipitation obtained at P_2 = atmospheric pressure
- X_{CO2}=0,16 (molar fraction of CO_2);
- Solid collected in a non-pressurized filter;
- Average diameter of particle: 740 nm;
- Total output of the solid collected: 86%.

Figure 6B is an image of a scanning electron microscope (SEM) of the ibuprofen compound obtained with PEG6000 and ΔP<0 (P2<P1).

- Ibuprofen/acetone/water/CO_2/PEG6000;
- Precipitation obtained at P_2 = atmospheric pressure
- X_{CO2}=0,16 (molar fraction of CO_2);
- Solid collected in a non-pressurized filter;
- Average diameter of particle: 680 nm;
- Total output of the solid collected: 81%.

From comparing Figures 6A and 6B it can be observed that with ΔP<0 the presence of the surfactant influences the size of the particle, reducing it with its presence.

Figure 6C is an image of a scanning electron microscope (SEM) of the ibuprofen compound obtained with PEG6000 and ΔP>0 (P2>P1).

- Ibuprofen/acetone/water/CO_2/PEG6000;
- Precipitation obtained at P2=147 bars and 35°C;
- X_{CO2}=0,16 (molar fraction of CO_2);
- Solid collected in a non-pressurized filter;
- Average diameter of particle: 935 nm;

[0055] Below, preferred embodiments of this invention are described, without limiting.

Examples

Example 1: Obtaining nanoparticles of ibuprofen through the process of the invention when ΔP<0 (without surfactant)

[0056] In a mixing reactor 7 of 300mL capacity, 170 mL of a solution of the ibuprofen compound in acetone with a relative concentration to saturation of 63% and 90mL of H_2O, obtaining a suspension of the drug in the acetone-water mixture. Over this suspension CO_2 is added with a volume of flow of 7Kg/hr until the pressure P_1 of reactor 7 reaches the 100Bar. The temperature is kept constant throughout the entire process at 35°C. At these conditions, this system is formed by a transparent microemulsion consisting of the system ibuprofen/acetone/water/CO_2. The microemulsion is left to stabilize at P1 and 35°C during 15 minutes (see Figure 2). The supply of CO_2 is closed and the adding of N_2 begins through the uppermost part of the reactor through valve 6, to maintain the pressure P1 constant at 100 bar within the reactor during the depressurization process of the microemulsion. The depressurization of the microemulsion from P1 to P2=1bar, with the consequent rapid evaporation of CO_2, is done through the opening of a valve 12. The evaporation of CO_2 causes the water to again manifest its new anti-solvent characteristic over the dissolved ibuprofen in the organic phase, causing its precipitation. The precipitated particles are collected in filter 13 at P2=1bar (atmospheric pressure). The precipitated particles are washed with CO_2 at 40Bar. The mother liquors are collected in container 15 through valve 14. The size of the particle of the ibuprofen compound was determined through a scanning electron microscope (SEM). The distribution of particle sizes of the collected solid phase in filter 13 have an average of 740 nm with a standard deviation of 100 nm. It was observed through X-ray powder diffraction that the particles obtained are crystalline, and by using the scanning electron microscope (SEM) that they have a homogenous spheroidal morphology (see Figure 5A). The output of the process is of 86%.

[0057] Optionally, there is a second filter to collect the possible solids that did not dissolve in the microemulsion obtained at pressure P1; said filter is represented in Figure 2 as filter **11**.

Example 2: Obtaining nanoparticles of ibuprofen through the process of the invention when ΔP<0 (in presence of a surfactant PEG6000 dissolved in the aqueous phase)

[0058] In a mixing reactor 7 of 300mL capacity, 170mL of a solution of the ibuprofen compound in acetone with a

relative concentration of 63% and 90mL of an aqueous solution which contains 10% in weight of the surfactant PEG6000, are introduced, obtaining a suspension of the drug in the acetone-water mixture. Over this suspension CO_2 is added with a volume of flow of 7Kg/hr until the pressure P1 of reactor 7 reaches 100bar. The temperature is kept constant throughout the entire process at 35°C. At these conditions, this system is formed by a transparent microemulsion consisting of the system ibuprofen/acetone/water/PEG6000/CO_2. The microemulsion is left to stabilize at P1 and 35°C during 15 minutes (see Figure 2). The supply of CO_2 is closed and the adding of N_2 begins through the uppermost part of the reactor 7 through valve 6, to maintain the pressure P1 constant at 100Bars within the reactor during the depressurization process of the microemulsion. The depressurization of the microemulsion from P1 to P2=1Bar, with the consequent rapid evaporation of CO_2, is done through the opening of a valve 12. The evaporation of CO_2 causes the water to again manifest its new anti-solvent characteristic over the dissolved ibuprofen in the organic phase, causing its precipitation. The precipitated particles are collected in filter 13 at P2=1bar (atmospheric pressure). The precipitated particles are washed with CO_2 at 40Bar. The mother liquors are collected in container 15 through valve 14. The size of the particle of the ibuprofen compound was determined through a scanning electron microscope (SEM). The distribution of particle sizes of the collected solid phase in filter 13 have an average of 680nm with a standard deviation of 110nm. It was observed through X-ray powder diffraction that the particles obtained are crystalline, and by using the scanning electron microscope (SEM) that they have a homogenous spheroidal morphology (see Figure 5B). The output of the process is of 81%.

[0059] Optionally, there is a second filter to collect the possible solids that did not dissolve in the microemulsion obtained at pressure P1; said filter is represented in Figure 2 as filter **11.**

Example 3: Obtaining nanoparticles of ibuprofen through the process of the invention when $\Delta P>0$ (without surfactant)

[0060] In a mixing reactor 7 of 300mL capacity, 170mL of a solution of the ibuprofen compound in acetone with a relative concentration of 63% and 90mL of H_2O are introduced, obtaining a suspension of the drug in the acetone-water mixture. Over this suspension CO_2 is added with a volume of flow of 7Kg/hr until the pressure P1 of reactor 7 reaches 100bar. The temperature is kept constant throughout the entire process at 35°C. At these conditions, this system is formed by a transparent microemulsion consisting of the system ibuprofen/acetone/water/CO_2. The microemulsion is left to stabilize at P1 and 35°C during 15 minutes (see Figure 2). The supply of CO_2 is closed and the adding of N_2 begins through the uppermost part of the reactor 7 through valve **6,** until a pressure P2=146Bar within the reactor (P2>P1) is reached. The increase in pressure from P1 to P2 stimulates the water to again manifest its new anti-solvent effect over the solute present in the system solute/organic solvent/water/CO_2, causing its precipitation. The precipitated solid is filtered over filter **11** at pressure P2. The precipitation of the mother liquors is done through valve **12** and they are collected in tank **15,** after passing through filter **13** and valve **14.** The solid collected in filter **11** is washed with CO_2 at 40Bar. The size of the particle of the ibuprofen compound was determined through a scanning electron microscope (SEM). The distribution of particle sizes of the collected solid phase in filter **11** have an average of 940nm with a standard deviation of 300nm. It was observed through X-ray powder diffraction that the particles obtained are crystalline, and by using the scanning electron microscope (SEM) that they have a homogenous spheroidal morphology. The output of the process is of 20%.

Example 4: Obtaining nanoparticles of ibuprofen through the process of the invention when $\Delta P>0$ (in presence of a surfactant PEG6000 dissolved in the aqueous phase)

[0061] In a mixing reactor 7 of 300mL capacity, 170mL of a solution of the ibuprofen compound in acetone with a relative concentration of 63% and 90mL of an aqueous solution which contains 10% in weight of surfactant PEG6000, are introduced, obtaining a suspension of the drug in the acetone-water mixture. Over this suspension CO_2 is added with a volume of flow of 7Kg/hr until the pressure P1 of reactor 7 reaches 100bar. The temperature is kept constant throughout the entire process at 35°C. At these conditions, this system is formed by a transparent microemulsion consisting of the system ibuprofen / acetone / water / PEG6000 / CO_2. The microemulsion is left to stabilize at P1 and 35°C during 15 minutes (see Figure 2). The supply of CO_2 is closed and the adding of N_2 begins through the uppermost part of the reactor 7 through valve **6** until a pressure P_2=146Bar within the reactor(P2>P1) is reached. The increase in pressure from P1 to P2 stimulates the water to again manifest its new anti-solvent effect over the solute present in the system solute/organic solvent/water/PEG6000/CO_2, causing its precipitation. The precipitated solid is filtered over filter **11** at pressure P2. The precipitation of the mother liquors is done through valve **12** and they are collected in tank **15,** after passing through filter **13** and valve **14.** The solid collected in filter **11** is washed with CO_2 at 40Bar. The size of the particle of the ibuprofen compound was determined through a scanning electron microscope (SEM). The distribution of particle sizes of the collected solid phase in filter **11** have an average of 935nm with a standard deviation of 460nm. It was observed through X-ray powder diffraction that the particles obtained are crystalline, and by using the scanning electron microscope (SEM) that they have a homogenous spheroidal morphology . The output of the process is of 21%.

(See Figure 6C)

Claims

1. Process for obtaining solid micro- or nanoparticles which comprises:

   a) preparing in a closed container a mixture that includes an organic solvent or a mixture of organic solvents, a solid compound C and water (H_2O),
   where in said stage a) there are at least one liquid phase and one solid phase,
   characterized in that it also comprises:
   b) adding a fluid B to said mixture prepared in stage a) so that the pressure of the container is increased until to reach a first pressure (P_1), allowing said addition of fluid B at said first pressure (P_1) to prepare a microemulsion of an organic phase saturated with water,
   where there is no solid phase in this stage and where at said first pressure (P1) the value of the predetermined supersaturation (β) of the solid compound C is lower to or equal to 1,
   c) varying said first pressure (P_1) to a second pressure (P_2), where said variation in pressure is different from zero ($\Delta P \neq 0$), and where at said second pressure (P_2) said water (H_2O) has an anti-solvent effect which cause the precipitation of solid micro- or nanoparticles of compound C with homogenous structure;
   where in said stage c) there are at least one liquid phase and one solid phase;
   and, if desired;
   d) collecting at said second pressure (P_2) said solid micro- or nanoparticles by conventional methods.

2. Process according to claim 1, where said stages a) and b) are carried out simultaneously.

3. Process according to any of the previous claims, where in stage a) the mixture includes a surfactant.

4. Process according to claim 1, where in stage a) said container is at atmospheric pressure and room temperature.

5. Process according to claim 1, where in stage c) said variation is such that the second pressure (P_2) is greater than (P_1), ($\Delta P>0$).

6. Process according to claim 5, where said stage c) is reversible, i.e., the precipitation is a reversible phenomenon.

7. Process according to claim 1, where in stage c) said variation is such that the second pressure (P_2) is lower than the first pressure (P_1), ($\Delta P<0$).

8. Process according to claim 1, where when $\Delta P>0$ said organic solvent is selected among a polar or non-polar solvent.

9. Process according to claim 1, where when $\Delta P<0$ said organic solvent is a polar solvent.

10. Process according to claim 1, where said solid compound C is insoluble or partially insoluble in H_2O.

11. Process according to claim 1, where said fluid B is CO_2.

12. Process according to claim 1, where said solid micro- or nanoparticles have a particle size of less than 10 μm, preferably of less than 1 μm.

13. Process according to claim 1, where said solid micro- or nanoparticles have an aspect ratio value close to the unity (1).

14. Process according to claim 13, where said micro- or nanoparticles have a substantially spheroidal morphology.

15. Process according to any of the previous claims, where given that solid compound C has a crystalline nature said micro- or nanoparticles obtained have a crystalline structure.

16. Composition which comprises said solid micro- or nanoparticles obtained according to any of the previous claims for preparing formulas together with other acceptable pharmaceutical exipients.

17. Use of said solid micro- or nanoparticles obtained according to any of claims 1 to 15 for the manufacture of a medicine for oral administration in aerosol form.

18. Use of said solid micro- or nanoparticles obtained according to any of claims 1 to 15 for manufacture of a suspension for oral intravenous or mucosal administration.

FIG 1

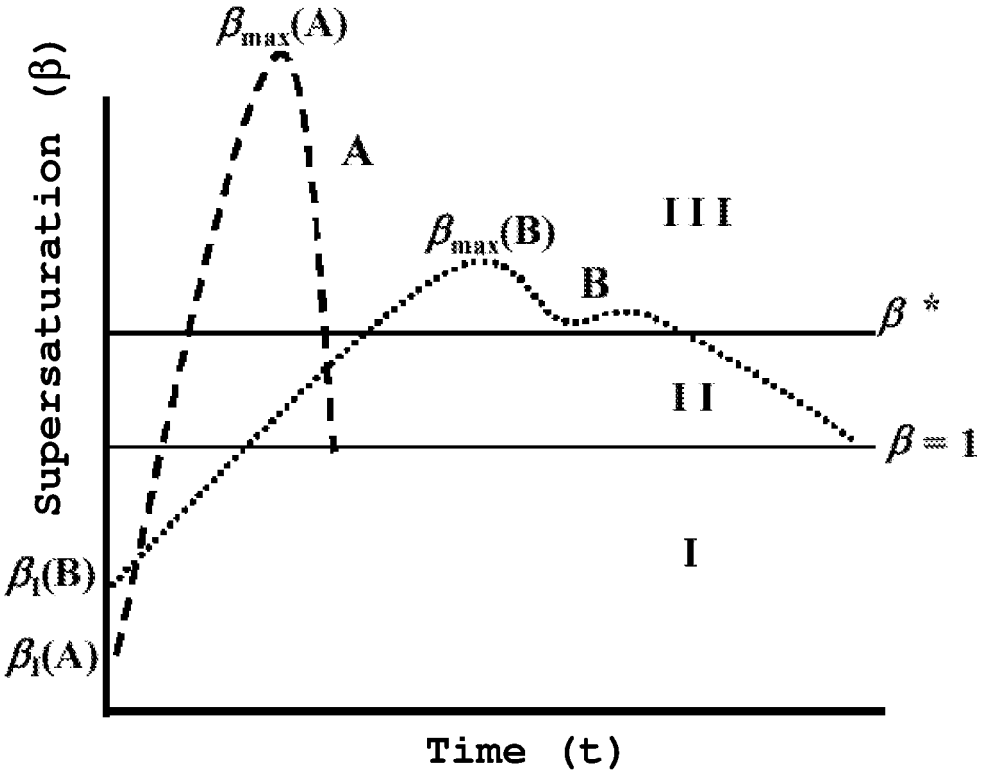

β_{max}(A)
A
β_{max}(B)
B
III
II
I
β *
β = 1
β_1(B)
β_1(A)
Supersaturation (β)
Time (t)

FIG 2

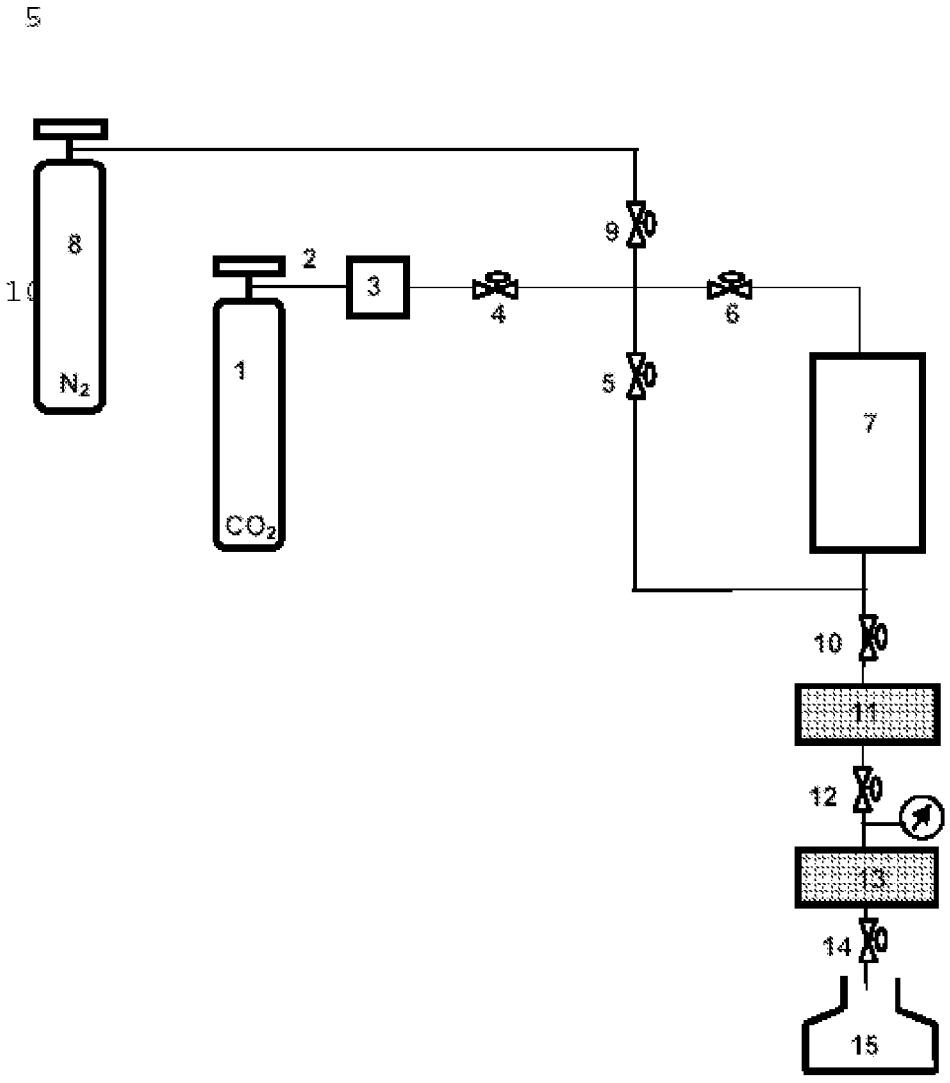
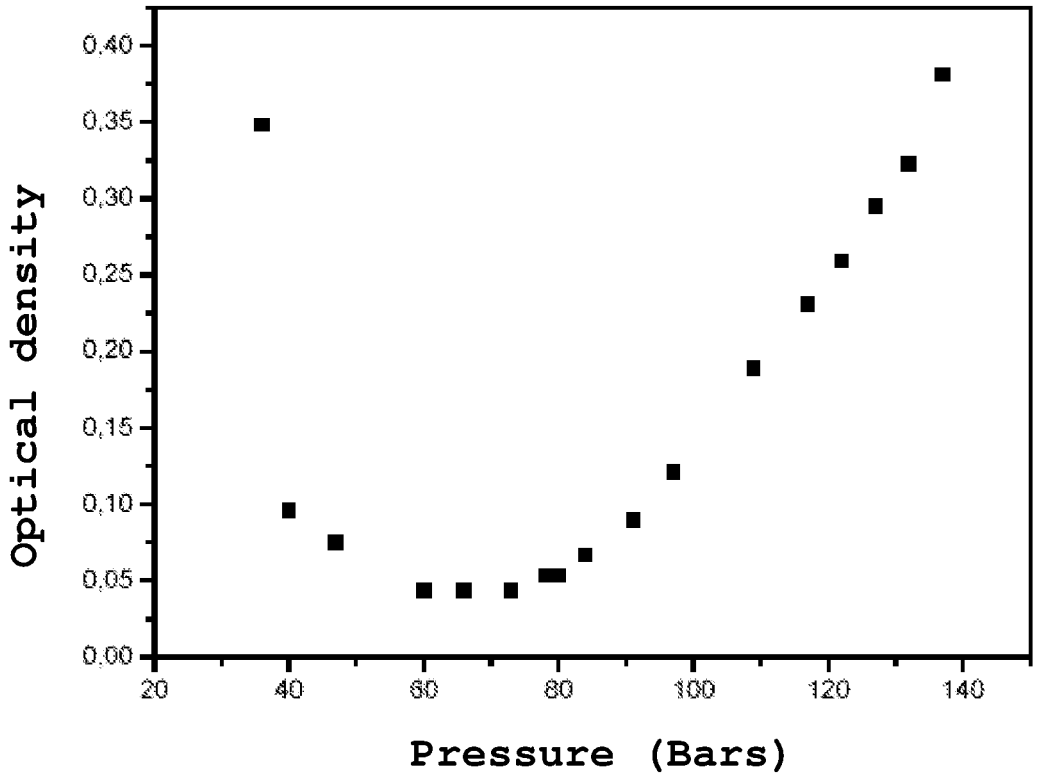


FIG 3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0,30
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0,20
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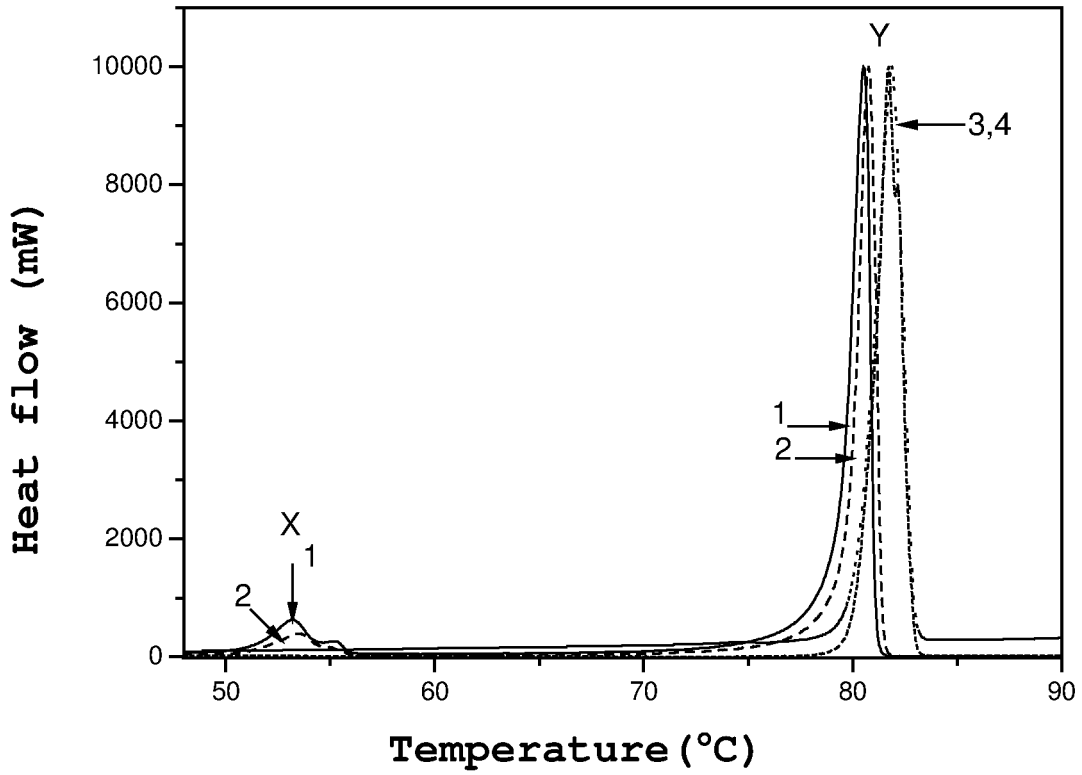
0,05
0,00
20
40
60
80
100
120
140
Pressure (Bars)

FIG 4


Heat flow (mW)
10000
8000
6000
4000
2000
0
50
60
70
80
90
Temperature(°C)
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1
2
Y
3,4
1
2

FIG 5

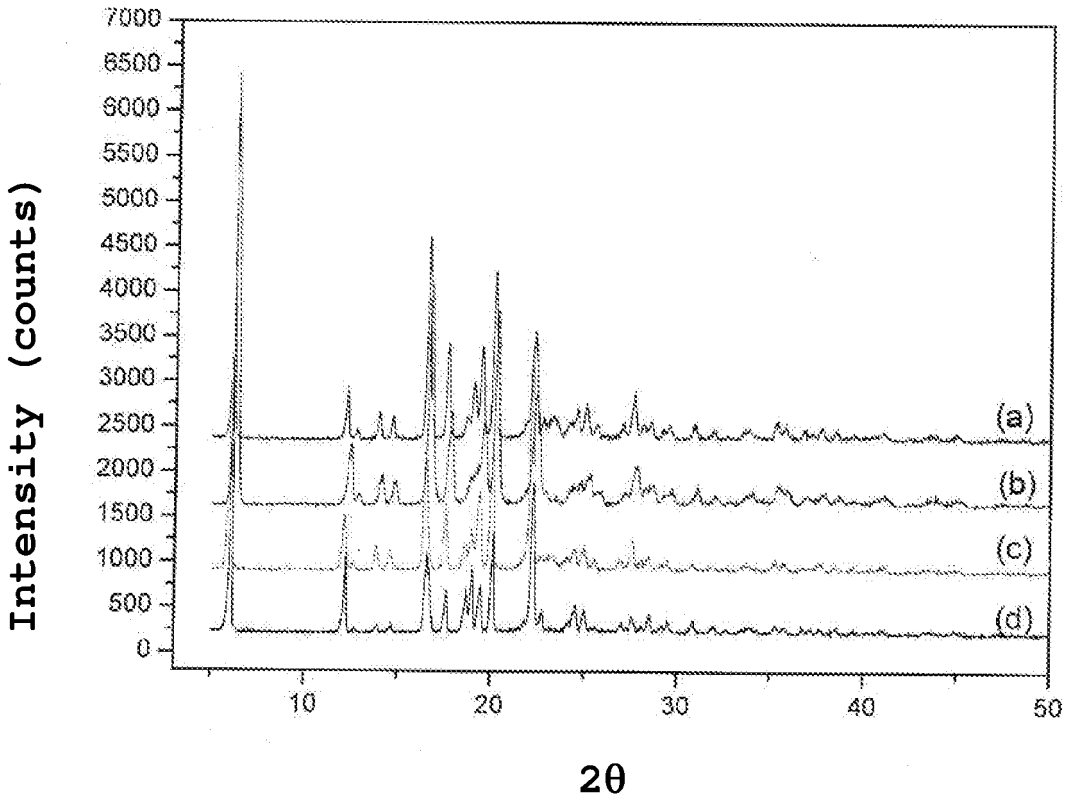

Intensity (counts)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
20
30
40
50
2θ
(a)
(b)
(c)
(d)

FIG 6A

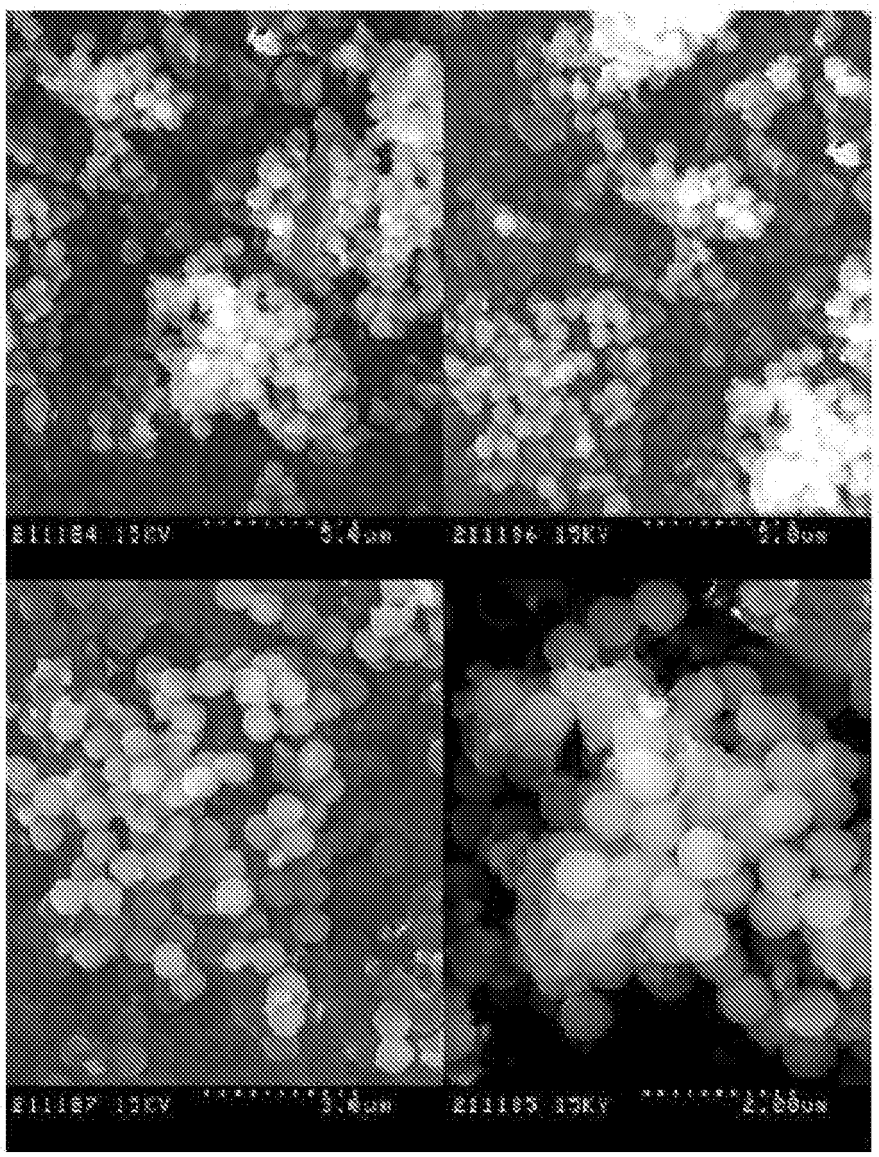
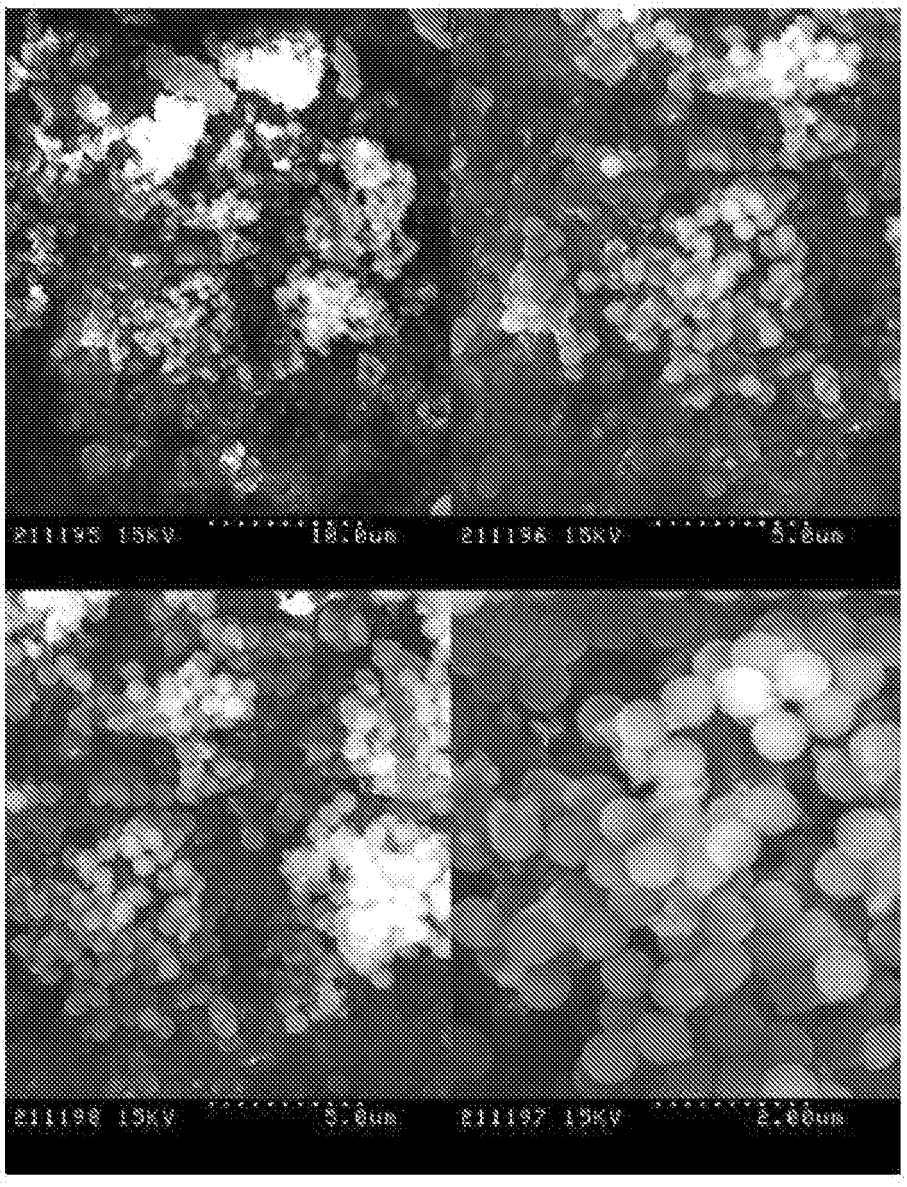


FIG 6B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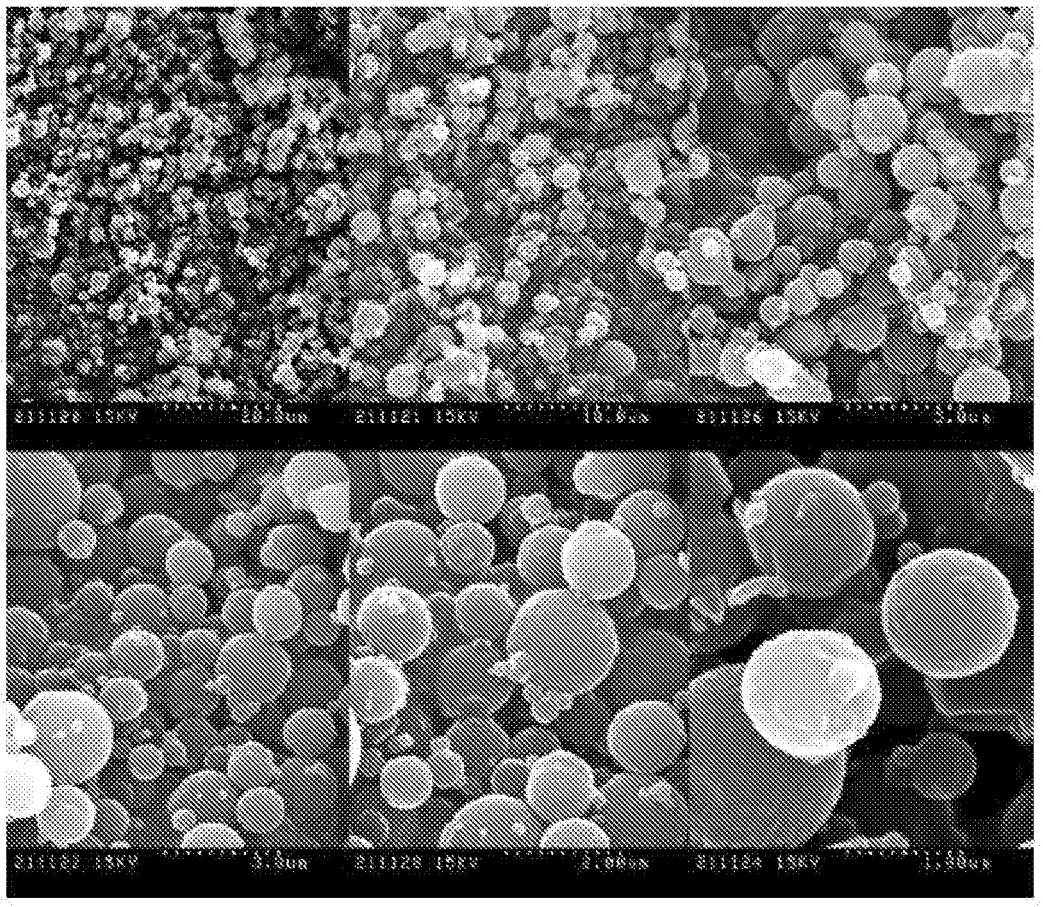
211196 15KV 5.0um
211198 15KV 5.0um
211197 15KV 2.00um

FIG 6C



INTERNATIONAL SEARCH REPORT

International application No.
PCT/ ES 2009/070485

A. CLASSIFICATION OF SUBJECT MATTER

see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01J, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

INVENES,EPODOC,WPI,TXTUS,XPESP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	ES 2170008 A1 (SOC ES CARBUROS METALICOS SA) 16.07.2002, column 3, lines 17-53; figure B.	1

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure use, exhibition, or other means
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other documents , such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2010 (25.01.2010)	**(29/01/2010)**
Name and mailing address of the ISA/ O.E.P.M. Paseo de la Castellana, 75 28071 Madrid, España. Facsimile No. 34 91 3495304	Authorized officer M. García González Telephone No. +34 91 349 53 15

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES 2009/070485

C (continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/ ES 2009/070485

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			11.01.2007
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/ ES 2009/070485

CLASSIFICATION OF SUBJECT MATTER

B01J 13/00 (2006.01)
A61K 9/14 (2006.01)
A61K 9/12 (2006.01)
A61K 9/10 (2006.01)

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